REMARKS

I. Status of the Claims

Claims 1-84 were originally filed. As the result of a restriction requirement, claims 1-4, 10, 50, and 55 are elected, whereas the remaining claims are withdrawn from consideration.

II. Claim Rejections

35 U.S.C. §103

Claims 1-3, 10, 50, and 55 remain rejected under 35 U.S.C. §103(a) for alleged obviousness over Wyatt (US2004/0109887) in view of Rovinski (U.S. Patent No. 5,866,320). Claims 1-4, 10, 50, and 55 also remain rejected under 35 U.S.C. §103(a) for alleged obviousness over Wyatt in view of Root (US2003/0082525). Applicants respectfully traverse the rejections.

A. No Prima Facie obviousness Is Established

In order to establish a *prima facie* showing of obviousness, three requirements must be satisfied: all limitations of a pending claim must be expressly or impliedly disclosed by prior art references; there must be a suggestion or motivation in the art for one skilled artisan to combine the limitations; and there must be a reasonable expectation of success in making such a combination. MPEP §2143.

The pending claims relate to a modified HIV envelope glycoprotein 160 (gp160) that has a gp120 subunit and a gp41 subunit, the C-terminus of gp120 covalently linked to the N-terminus of gp41 via a heterologous peptide linker of at least 5 amino acids. As explained in Applicants' previous responses, Wyatt describes a gp160ΔCT containing two Arg → Ser mutations (which abolish the proteolytic cleavage to generate gp120 and gp41) but does not describe or suggest the use of any linker between gp120 and gp41, particularly any peptide linker having the features specified in the pending claims. The two secondary references, Rovinski and Root, are apparently cited for the purpose of providing the limitation of a peptide linker: Rovinski teaches the use of a peptide linker containing a heterologous antigenic epitope in a

recombinant non-infectious retrovirus-like particle so as to allow the distinction of this recombinant particle from other retroviruses; Root teaches the construction of a 5-helix protein using a peptide linker containing the GGSGG sequence. Applicants contend that no *prima facie* obviousness is established, at least for the reason that the Examiner has not identified, either in general or in the cited references, any motivation or suggestion to combine the claim limitations.

Wyatt teaches substitution of the two Arg residues within the protease cleavage site so that the resulting gp160ΔCT cannot undergo proteolysis at this site. While making the obviousness rejections, the Examiner asserts that placing a peptide linker, such as one described by Rovinski *et al.*, between gp120 and gp41 is motivated by an artisan's desire "to differentiate between infection by HIV or another retrovirus such as non-infectious, retrovirus-like particle" (see page 4 of the Office Action mailed February 22, 2007). The advantage of a Rovinski's linker in having a distinct antigenic epitope is, however, irrelevant to this invention, because a peptide linker is used in this invention to provide a flexible tether between gp120 and gp41, not an identifying marker. Thus, the Examiner has identified no motivation in Wyatt or Rovinski to combine the teaching of the two references.

The Examiner also contends that the motivation to use a linker such as one described by Root *et al.* exists because an artisan would want to "increase the flexibility of the linker" and to "preserve and ... stabilize the native conformation of the gp120-gp41 complex" (see page 5 of the Office Action). Yet, these alleged motivations find no specific basis in the teaching of the cited references when viewed together. Nowhere in Wyatt have the authors mentioned any reason that might prompt one to consider the strategy of inserting a peptide linker to disrupt the protease cleavage site as an alternative to the point mutations in gp160ΔCT. Nor has the Examiner pointed out where in Wyatt can one find any discussion regarding the importance of linker flexibility and preservation of gp120-gp41 conformation. The Root *et al.* reference clearly provides no such specific suggestions either.

It is well settled in the prevailing case law that the obviousness determination must be made when the claimed invention is considered as a whole, the references are considered

as a whole, and the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. See, *e.g.*, *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187n5 (Fed. Cir. 1986), and MPEP §2141 II. Applicants contend that, since the generalized advantages of using a peptide linker between gp120 and gp41 as alleged by the Examiner find no specific basis in the cited references, these advantages are nothing more than a motivation or suggestion that became apparent only in the hindsight afforded by the present invention. Such alleged advantages thus cannot be relied on as the motivation or suggestion necessary for establishing a *prima facie* case of obviousness.

Applicants thus contend that no *prima facie* obviousness is established.

B. The gp120-gp41 Conjugate of This Invention Has Unexpected Properties

Even assuming, for the sake of argument, that a *prima facie* showing of obviousness could be made (which Applicants contend has not been made), the obviousness rejection should not be sustained because the gp120-gp41 conjugate of this invention has surprising properties that simply cannot be expected or gleaned from the combined teaching of the cited references.

To demonstrate this point, Applicants present a publication by Chow *et al.* (*Biochemistry* 2002, **41**:7176-7182, attached as **Exhibit A**), which describes the work of the inventors relating to conjugates of gp120 and gp41, joined by peptide linkers of varying lengths. It is reported in this publication that peptide linkers of relatively longer lengths render increased flexibility to the resultant gp120-gp41 conjugates. The increased flexibility in turn permits the conjugates to assume the native conformation of the gp120-gp41 complex, exposing conserved structures in these viral proteins that are critical for the binding between the viral proteins and cellular surface receptors and therefore critical for viral entry into host cells. In fact, the inventors observed that gp120-gp41 conjugates containing longer linkers (such as 15 and 26 amino acids) are about100 times more potent as viral entry inhibitors than conjugates containing shorter linkers (such as 4 amino acids). See, *e.g.*, ABSTRACT on page 7176 and Discussion on

page 7180. Such a dramatic increase in efficacy is simply not something one would have or could have expected by combining the teaching of Wyatt with that of Rovinski or Root.

Thus, even if a *prima facie* obviousness is established (which Applicants contend has not been established), it is rebutted by the unexpected properties of the gp120-gp41 conjugates of this invention, namely their exceptionally high potency as viral entry inhibitors.

In summary, Applicants contend that the Examiner has not made a *prima facie* showing of obviousness. Even assuming such a showing had been made, it would be rebutted by evidence presented in Exhibit A that the gp120-go41 conjugate of this invention has surprising properties that cannot be expected or gleaned from the cited references or knowledge in the art. As such, Applicants respectfully request that the obviousness rejections under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachment (Exhibit A: Chow *et al.*, *Biochemistry* 2002, **41**:7176-7182)
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